Remarks

This Amendment is being filed in response to the Office Action dated March 21, 2007. Claims 1-20 and 26-32 were pending in the subject application. By this Amendment, Applicants have amended claims 1, 15, 16, 18 and 26 and canceled claims 11, 14 and 20 without prejudice or disclaimer. Applicants maintain that the amendments to claims 1, 15, 16, 18 and 26 raise no issue of new matter. Accordingly, upon entry of this Amendment, claims 1-10, 12, 13, 15-19 and 26-32, as amended, will be pending and under examination.

Claim Objection and Allowable Subject Matter

On page 2 of the Office Action, the Examiner objected to claims 1-10, 12-20 and 26-32 for containing non-elected subject matter. The Examiner indicated that claims 1-10, 12-20 and 26-32 are allowed in so far as they read on the elected subject matter.

In response, applicants have amended claims 1, 15, 16 and 18 to the elected subject matter and canceled claims 11, 14 and 20 without prejudice or disclaimer to pursue the non-elected subject matter in a future divisional or continuation application. Applicants have further amended claim 26 to an independent claim by incorporating the elements of previous claim 20, which has been canceled. Accordingly, applicants respectfully request that the objection of these claims be reconsidered and withdrawn.

Claim Rejection under 35 USC §112

On pages 2 and 3 of the Office Action, the Examiner rejected claims 20 and 26-32 under 35 USC 112, first paragraph, alleging that the specification, while being enabling for the treatment of one disease or disorder and does not reasonably provide enablement for the prevention and treatment of all the diseases listed in the claims. The Examiner further alleged that it is established that in the art that these disorders are not preventable and that it is conventional knowledge in the art that one compound has only one major use or that in can only be used to treat one disorder at a given time.

Without conceding the correctness of the Examiner, the rejection of claim 20 is moot because this claim has been canceled without disclaimer or prejudice to pursue the subject matter of this claim in a future continuation application. Furthermore, Applicants have amended previous

claim 26 to an independent claim. Applicants reserve the right to pursue the subject matter directed to the prevention of said disorders in a future continuation application. Claims 27-32 remain dependent on claim 26.

Regarding claims 26-32, Applicants maintain that one of ordinary skill in the art would understand how to make and use the claimed compounds in the methods of treating a central nervous system disorder selected from the group consisting of a seizure disorder, a neuropathic pain disorder, a migraine pain disorder, an anxiety disorder, a neurodegenerative disorder and a neuronal hyperexcitation state disorder based on the disclosure of the specification.

Applicants maintain that the nexus between KCNQ channel openers and the treatment of the disorders being claimed is established in the scientific community as evidenced by the peer-reviewed articles and patent applications referenced in the specification. See Specification, p. 2, line 9 through page 5, line 3. The disclosures which provide the enablement of the claimed methods of treating the above-identified disorders of claims 26-32 are discussed below.

- **Seizure Disorder**: Applicants maintain that the nexus between human KCNQ channel openers and the treatment of a seizure disorder such as convulsion, epilepsy or a status epilepticus is established in the scientific community. For example, Wickenden, et al. *Molecular Pharmacology*, 2000, 58, 591-600 (copy enclosed) is cited at page 2, line 33 through page 3, line 4 of the specification, and discloses that the activation of KCNQ2/3 channels may be responsible for at least some of the anticonvulsant activity of Retigabine, a compound which enhances activation of KCNQ2/3 channels, and that other agents working by the same mechanism may have similar effects. The article concludes by asserting that "our findings, coupled with the recent genetic evidence linking KCNQ2/3 channel mutations with benign familial neonatal epilepsy, strongly suggest that KCNQ2/3 channels may represent novel targets for antiepileptic drugs." Additionally, Tober, et al. *European Journal of Pharmacology*, 1996, 303, 163-169 (copy enclosed) is cited at page 3, lines 28-31 of the specification, and discloses that Retigabine has also been shown to delay the progression of hippocampal kindling in a model of epilepsy development which further suggests that activation of KCNQ2/3

channels and that of other agents working by the same mechanism may have similar effects.

- **Neuropathic Pain Disorder**: Applicants further maintain that the nexus between human KCNQ channel openers and the treatment of a neuropathic pain disorder such as allodynia, hyperalgesic pain, phantom pain, neuropathic pain related to diabetic neuropathy or neuropathic pain related to migraine is established in the scientific community. For example, Wickenden, et al. *Society for Neuroscience Abstracts* 2002, 454.7 (copy enclosed) is cited at page 3, lines 6-11 of the specification, and discloses that KCNQ2/3 channels are upregulated in models of neuropathic pain and the authors conclude that "KCNQ channels may represent targets for novel analgesic agents for the treatment of pain associated with nerve injury."

- **Migraine Pain Disorder**: Applicants maintain that the nexus between human KCNQ channel openers and the treatment of a migraine pain is established in the scientific community. For example, Goldstein, et al. *Society for Neuroscience Abstracts* 2002, 53.8 (copy enclosed) is cited at page 3, lines 15-18 of the specification, and discloses the localization of KCNQ subunits in the trigeminal and dorsal root ganglia and also in the trigeminal nucleus caudalis and the effects of a novel non-selective KCNQ opener on the regulation of activity of first and second order neurons. The authors conclude these data suggest that a KCNQ opener inhibits activity of first and possible second order neurons in the trigeminal circuitry involved in migraine pain transmission, and that pharmacological activation of KCNQ channels may be useful as a new method of headache treatment.

- **Anxiety Disorder**: Applicants further maintain that the nexus between KCNQ channel openers and the treatment of anxiety disorders such as a anxiety, a generalized anxiety disorder, panic anxiety, an obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, an acute stress reaction, an adjustment disorder, a hypochondriacally disorder, a separation anxiety disorder, agoraphobia, a specific phobia, an anxiety disorder due to a general medical condition or a substance-induced anxiety disorder is established in the scientific community. For example, Saganich, et al. *Journal*

of Neuroscience 2001, 21, 4609-4624 (copy enclosed) is cited at page 4, lines 6-11, and discloses that the mRNA localization for KCNQ 2/3 receptors subtypes are found in brain regions associated with anxiety and emotional behaviors which suggests the participation of these receptors in anxiety. Accordingly, it is expected that KCNQ channels may be useful for the treatment of anxiety disorders.

- **Neurodegenerative and Neuronal Hyperexcitation State Disorders**: Applicants maintain that the nexus between KCNQ channel openers and the treatment of neurodegenerative disorders such as Alzheimer's disease, Huntington's chorea, multiple sclerosis, amyotrophic lateral sclerosis, AIDS-induced encephalopathy, an infection-related encephalopathy, Creutzfeld-Jakob disease, Parkinson's disease or trauma-induced neurodegeneration and neuronal hyperexcitation state disorders such as are established in the scientific community. Regarding neurodegenerative disorders, Noda, et al. *Society for Neuroscience Abstracts* 2003, 53.9 (copy enclosed) is cited at page 8, lines 20-24, and discloses that mRNA for KCNQ 3 and 5 as well as KCNQ2 receptor subtypes are expressed in glial cells in the brain and asserts that these results suggest that KCN channel openers may have neuroprotective effects. With respect to neurodegenerative disorders and neuronal hyperexcitation state disorders, Applicants respectfully direct the Examiner's attention to PCT International Publication No. WO 97/15300, which is cited at page 4, line 30 through page 5, line 3 of the specification. Applicants note that the U.S. counterpart for this international application is U.S. Patent No. 5,852,053. This application describes the use of Retibagine, an activator of KCNQ 2/3 channels, to treat neuronal hyperexcitation state such as medicament withdrawal or by intoxication.

Furthermore, the Examiner asserted that it is conventional knowledge in the art that one compound has only one major use or that it can only be used to treat one disorder at a given time.

In response, Applicants respectfully disagree with the Examiner's assertion that it is conventional knowledge in the art that one compound has only one major use or that it can only be used to treat one disorder at a given time. In fact, there are several currently marketed drugs which are used to for several major uses. For example, Cymbalta® is approved by the Federal Drug Administration

(FDA) to treat (1) Major Depressive Disorder; (2) Diabetic Neuropathic Pain; and (3) Generalized Anxiety Disorder. See Cymbalta® labeling at p. 10 (copy attached as Exhibit A). Furthermore, Applicants note that the active pharmaceutical ingredient in Cymbalta® (Duloxetine hydrochloride) is approved in Europe by the European Agency for the Evaluation of Medicinal Products (EMEA) to treat Stress Urinary Incontinence and is marketed in Europe as Yentreve®. See Yentreve® Summary of Product Characteristics at p. 2 (copy attached as Exhibit B).

In view of the foregoing, Applicants respectfully maintain that the above-described disclosures are representative of the state of the art with respect to uses of the KCNQ channels and the predictability of KCNQ channel openers for treating a central nervous system disorder selected from the group consisting of a seizure disorder, a neuropathic pain disorder, a migraine pain disorder, an anxiety disorder, a neurodegenerative disorder and a neuronal hyperexcitation state disorder. Applicants maintain that claims 26-32 are fully enabled by the specification and the Examiner has not established a prima facie case of non-enablement. Accordingly, Applicants respectfully requests that this rejection be withdrawn and that all pending claims be allowed.

Supplemental Information Disclosure Statement

In order to ensure compliance with applicants' duty of disclosure under 37 C.F.R. §1.56 and §1.97(a)-(d), applicants request that the following references be considered and made of record in the above-identified application.

1. WICKENDEN, et al. "Retigabine, A Novel Anti-Convulsant, Enhances Activation of KCNQ2/Q3 Potassium Channels" Molecular Pharmacology, 2000, 58, 591-60;
2. TOBER, et al. "D-23129: a potent anticonvulsant in the amygdala kindling model of complex partial seizures" European Journal of Pharmacology, 1996, 303, 163-169;
3. WICKENDEN, et al. "KCNQ Channel Expression in Rat DRG Following Nerve Ligation" Society for Neuroscience Abstracts, 2002, No. 454.7;
4. GOLDSTEIN, et al. "Localization of KCNQ and KCNE Channel Subunits in the Central and Peripheral Nervous System of the Rat" Society for Neuroscience Abstracts, 2003, No. 53.8;

5. SAGANICH, et al. "Differential Expression of Genes Encoding Subthreshold-Operating Voltage-Gated K+ Channels in Brain" The Journal of Neuroscience, 2001, 21, 4609-462; and

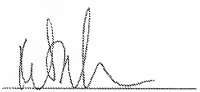
6. NODA, et al. "KCN Channels in Glial Cells" Society for Neuroscience Abstracts, 2003, No. 53.9.

Copies of references 1-6 are enclosed herewith. It is respectfully requested that the Examiner consider the cited references and that copies of the enclosed Form PTO/SB/08b be initialed and returned indicating that such information has been considered. Applicants respectfully request that the Examiner make the cited references of record in the subject application.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that the pending claims be allowed and the case passed to issue. If there are any issues remaining that the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is requested to contact the undersigned at the telephone number indicated below. No fees other than the $120.00 fee for a one-month extension of time and the $180.00 fee for filing of a Supplemental Information Disclosure Statement are deemed necessary and authorization is hereby given to charge these amounts to Deposit Account No. 503201. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 503201.

Respectfully submitted,



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